REMARKS

Applicants respond below to the specific rejections and objections raised by the Examiner in the Final Office Action of March 20, 2003.

I. Objections to the Specification

The Examiner has objected to the specification on the grounds that there are two tables labeled "Table 6." Applicants thank the Examiner for bringing the issue to Applicants' attention. Applicants have amended the specification to renumber the tables correctly. Instances in the specification where each table was cited have also been amended to refer to the correct table number.

II. Objections and Rejections under 35 U.S.C. § 101

Claims 27, 28, and 32-35 stand rejected under 35 U.S.C. § 101 for allegedly lacking specific, substantial, and credible asserted utility or a well established utility. For the reasons set forth below, Applicants respectfully traverse.

The Examiner has quoted Applicants arguments in a previous response that the "diluted samples were used provided that the Ct value of the normal human DNA subtracted from test DNA was +/- 1 Ct." The Examiner then correctly reiterates Applicants arguments that "a ΔCt value of 1 indicates that the sample had a two-fold amplification of the test sequence as compared to the control." However, the Examiner follows that statement with

> However, as stated in applicants arguments, the samples were considered to be "comparable" if the normal and test DNA had Ct values of ±1, i.e. a ΔCt value of 1. Accordingly, a ΔCt value of 1 cannot be considered to be a significant difference.

The Office Action, page 2, lines 1-3.

It appears that the Examiner has misunderstood Applicants' arguments. First, Applicants cannot find where in their previous arguments they stated that having a ΔCt of 1 would render the test DNA and the normal DNA "comparable." Applicants sincerely seek the Examiner's guidance in locating this argument, since this argument is erroneous and Applicants wish to correct the record. A ΔCt of 1 between the test DNA and the normal DNA does not render the

p. 4 of Paper 12 "comparable" is misquote, but concept is there - they can be compared if ± 1 Ct

two samples "comparable." In fact, this value indicates an *abnormal* DNA, one that the methods of the present invention correlate with cancerous tissue.

Second, the Examiner has taken Applicants' above-quoted statement that the samples were used when the ΔCt value was ±1 to mean that the experimental error for this procedure is ±1. This is not correct. A ΔCt value of 1 was used as a threshold number to screen out abnormal test samples from normal ones for further analysis. Thus, not only is ΔCt of 1 not within the experimental error, but it is significant enough that it is used as the gate-keeper value for separating normal from abnormal test samples. Therefore, the literal meaning of Applicants' statement is that diluted samples can be used with the methods of the present invention, provided that the diluted sample shows a ΔCt of at least 1 when the test sample and the normal DNA sample are compared.

Are they saying they pre-screened for desired data?

The Examiner then objects to the Applicants' reporting of measurements of hundredths of PCR cycle when they report ΔCt values. The Examiner further sates that the significance of difference of 1 or 2 PCR cycles is not clear since, according to the Examiner, "the ΔCt values of approximately 1 are of questionable significance, and it is not clear what the experimental error is."

Applicants respectfully point out that what the Examiner is objecting to is not Applicants' invention; the Examiner is objecting to a well-defined and prevalent methodology used in the art. Applicants have submitted herewith a declaration of Dr. Audrey Goddard with exhibits A-G (the Goddard Declaration), submitted in a related and co-owned patent application, Serial No. 09/903,925. As Dr. Goddard's *curriculum vitae*, Exhibit A of the Goddard Declaration, shows, she is an expert in the art of identifying and quantifying the amplification of oncogenes in cancers.

In her declaration, Dr. Goddard states that

> the quantitative TaqMan PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is

> useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

The Goddard Declaration, paragraph 7. Therefore, according to Dr. Goddard, a 2-fold increase, i.e., a ΔCt value of 1, not only is not of questionable significance, but is "significant and useful" in, *inter alia*, detecting cancerous tumors or the diagnosis of cancer. Thus, the Goddard Declaration support Applicants' position that the ΔCt value of 1 is significant and is outside of the experimental error of this procedure.

References attached to the Goddard Declaration as Exhibits B-G describe the state of the art of quantitation by TaqMan PCR techniques in great detail. For example, Exhibit C of the Goddard Declaration, Heid et al., "Real Time Quantitative PCR," *Genome Res.* 6:986-994 (1996), describes how Ct values are calculated. Following the procedure set forth in this reference, a Ct value to the nearest hundredth place is obtained. In fact, the reference itself reports Ct values to the hundredths place (see, for example, Table 1). Therefore, not only is it clear how Ct values reported to the hundredths place are possible, but such reporting is the standard in the field.

The Examiner then states that a positive result using the methods of the present invention may be due to aneuploidy of cancer cells, as opposed to the upregulation of test DNA. Applicants respectfully submit that this issue is irrelevant. The present Applicants have not set out to identify and distinguish the molecular base cause of cancer. Instead, one aspect of the present invention involves the determination of whether a particular tissue is cancerous or not. Whether the presence of extra genetic material is due to aneuploidy, that the Examiner concedes is unique to cancer cells, or due to upregulation of certain genes, is immaterial. In either case, what is detected is cancerous tissue. Thus, the methods disclosed in the present application and the subject matter of the claims are useful in the diagnosis of cancer, regardless of the molecular cause of the increase in oncogene expression.

No, it is not.

In view of the above, Applicants respectfully submit that the disclosure of the present application satisfies the utility requirements of 35 U.S.C. § 101. Consequently, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

III. Rejections under 35 U.S.C. § 112, First Paragraph

Claims 27, 28, and 32-35 stand rejected under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner alleges that since the claimed invention is not supported by an asserted utility, then a skilled artisan could not use the claimed invention. Applicants respectfully submit that in view of the above discussion a specific, substantial, and credible utility has been asserted for the claimed invention. As a result, this rejection is now moot. Applicants respectfully request that the Examiner withdraw the rejection.

IV. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 33-34 stand rejected under 35 U.S.C. § 112, second paragraph. Applicants have amended Claim 33 to depend from Claim 27, which is still pending. In view of this amendment, Applicants respectfully request that the Examiner withdraw the rejection.

V. Rejections under 35 U.S.C. §§ 102 and 103

Claims 27, 28, 32, and 35 stand rejected under 35 U.S.C. §§ 102 and 103. Applicants respectfully submit that since a proper assertion of utility has been made, Applicants are entitled to their claim of priority to December 1, 1999, the filing date of the International Application Serial No. PCT/US99/28634, and to February 11, 2000, the filing date of the International Application Serial No. PCT/US00/03565. Thus, the Strausberg and Furukawa references, having a publication date after the priority date of the present application, are removed as prior art, and all rejections based on these two references are now moot.

Furthermore, since neither Fransen reference discloses the full-length amino acid sequence of SEQ ID NO:2, the pending claims are novel over these cited references. In addition, since the Examiner has not provided any motivation or suggestion in the references themselves or the general knowledge in the art to modify the sequences of the cited references in order to obtain the sequences of the present invention, a prima facie case of obviousness has not been established.

Applicants, therefore, request that the Examiner reconsider and withdraw the rejections based on 35 U.S.C. §§ 102 and 103.

CONCLUSION

Applicants respectfully maintain that claims are patentable and request that they be passed to issue. No fee is believed due in connection with this response. If this is incorrect, the Commissioner is hereby authorized to charge Deposit Account No. 11-1410. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Respectfully submitted,

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Dated: May 19, 2003

By: _____

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